ATTACHMENT B

REMARKS

By the present amendment, minor amendments have been made to Claims 1, 11, 12, 22, 23, 29, 30 and 36, and in addition, the subject matter of Claims 5-10, which has been previously deemed allowable, has been rewritten as new Claims 54-56. New Claims 54-56 also incorporate the subject matter of Claims 38-40 which have now been canceled without prejudice. Finally, new Claims 42-53 have been added which repeat the method steps of the composition claims of issued U.S. Pat. No. 6,692,739, and thus these claims should be patentable as well. In light of the present amendments to the claims and the arguments as set forth herein, Applicants submit that the present case is in condition for allowance for the reasons stated below.

In the Official Action, the Examiner indicated that the subject matter of Claims 5 and 7-10 was allowable, and this indication of Allowability is acknowledged with appreciation. Applicants have rewritten Claims 5-10 as new Claims 54-56, which also includes the subject matter of Claims 38-40, but rewritten to avoid the Examiner's objections to those claims. It is thus submitted that Claims 54-56 are allowable in that they include the allowed subject matter of canceled Claim 5 and its dependent claims.

In the Official Action, Claims 22, 29 and 36 were rejected under 35 U.S.C. §102(b) as being anticipated by the Foster et al. patent, U.S. Pat. No. 6,008,341. However, the Examiner acknowledged that this reference did not disclose a human immunoglobulin composition, and now the composition claims of the present application are all directed to human immunoglobulin. Accordingly,

without addressing the merits of the Examiner's comments regarding this rejection, Applicant submits that the Examiner's prior rejection on the basis of the Foster patent, insofar as applied to the claims as amended, is respectfully traversed and should be withdrawn.

In the Official Action, Claims 11, 22, 29 and 36 were rejected under 35 U.S.C. §102(b) as being anticipated by the Gristina patents, U.S. Pat. Nos. 5,707,627 and 5,718,899. The Examiner argued that the compositions disclosed in Gristina "inherently" comprised antibodies directed to surface associate proteins, but recognized that the specific proteins, in particular ClfA, was not specifically disclosed in the Gristina patents. Instead, the Examiner asserted that while prior references showed that there are *S. aureus* strains which do not have clumping factor (as was reported in the prior Wickelhaus and Nicholas references), there would still be 99.3% of the *S. aureus* strains which included clumping factor, thus indicating it was likely that the non-specific whole cell preparations of Gristina would include antibodies to ClfA.

However, this is not the case, and the Examiner has substantially understated the number of strains of *S. aureus* which do **not** express ClfA. This fact is pointed out in the cited Kuusela U.S. Pat. No. 5,496,706 wherein tests were undertaken to determine the presence of clumping factor A or protein A in *S. aureus*, and the results showed that 11 out of 79 strains **were negative** for clumping factor A and protein A (it was not disclosed how many strains were negative to clumping factor alone, a number that would add to the total percentage of strains not expressing ClfA). See Column 5, lines 12-15.

Accordingly, these tests confirmed that a substantial number of *S. aureus* strains, at least 14% or higher, do not express ClfA, and even more strains which do express ClfA may not do so in such a way that it generates antibodies in the first place. Thus, in addition to the fact that Gristina does not disclose or suggest immunoglobulin compositions with high titers to specific surface proteins such as ClfA, it is in fact not inherent that such compositions would result with high titers to ClfA or the other adhesins as set forth in Applicants' invention, particularly in light of the fact that many strains do not even contain particular proteins such as ClfA. The Gristina patent therefore does not disclose or suggest the composition claims of the present application.

Accordingly, the Examiner's rejection on the basis of the Gristina references, insofar as applied to the claims as amended, is respectfully traversed and should be withdrawn.

In the Official Action, Claims 1-4, 6[1], 12-17, 22, 23-28, 29, 30-35, 36, 37, and 38-41 were rejected under 35 U.S.C. § 103 on the basis of the Hook et al. patent, U.S. Pat. No. 6,288,214. In short, while the Examiner acknowledged that the reference relates to the collagen binding protein and production of antibodies thereto, the Examiner also referred to unrelated sections from different parts of the reference in order to assert that these differing sections, none of which disclose a human immunoglobulin composition containing high titers to specific staphylococcal adhesins such as ClfA, combined to make the Applicants' claims

[1] In light of the fact that the Examiner considered Claim 5 to be allowable, and the fact that Claim 6 depended directly upon Claim 5, it is not clear why this claim was rejected in this rejection. In

obvious. In short, the Hook patent does not disclose human immunoglobulin compositions with high titers to specific staphylococcal adhesins such as ClfA, nor does it provide any motivation or suggestion to do so, and thus this rejection is respectfully traversed for reasons as stated in more detail below.

As an initial matter, Applicants have now reviewed the portions of the Hook patent cited by the Examiner, and it is clear that those passages do not support the Examiner's position that the Hook reference suggests Applicants' claimed invention. For example, the Examiner cites to Col. 12, lines 46-52 for the proposition that "humans are immunized with the peptide antigens disclosed therein for the purposes of generating an immune response." However, the actual passage not only reflects simple immunization, it is entirely directed to the use of collagen binding protein (CBP) and thus suggests at most that CBP's can be used as vaccines. Indeed, this entire passage, including the passage referred to by the Examiner, reads as follows:

> Antibodies may be of several types including those raised in heterologous donor animals or human volunteers **immunized with CBPs,** monoclonal antibodies (mAbs) **resulting from hybridomas derived from fusions of B cells from CBP-immunized animals** or humans with compatible myeloma cell lines, so-called "humanized" mAbs resulting from expression of gene fusions of combinatorial determining regions of mAb-encoding genes from heterologous species with genes encoding human antibodies, or **CBP-reactive antibody-containing fractions** of plasma from human donors. It is contemplated that any of the techniques described above might be used for the vaccination of subjects for the purpose of antibody production. Optimal dosing of such antibodies is highly dependent upon the pharmacokinetics of the specific antibody population in the particular species to be treated. It is contemplated that the duration of dosing **maintaining anti-CBP** levels at these inhibitory antibody concentrations would be for at least four to eight weeks following presumptive exposure to S. aureus, or throughout the

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any event, Claim 5 has been rewritten as Claim 54, and the subject matter of Claim 6 is now reflected in Claim 56 which is dependent upon new Claim 54 and should thus also be allowable.

duration of symptoms of disease and for at least four to eight weeks after cessation of these symptoms.

Using the peptide antigens described herein, the present invention also provides methods of generating an immune response, which **methods generally comprise administering to an animal, a pharmaceutically-acceptable composition comprising an immunologically effective amount of a CBP peptide composition**. Preferred animals include mammals, and particularly humans. Other preferred animals include murines, bovines, equines, porcines, canines, and felines. **The composition may include partially or significantly purified CBP peptide epitopes**, obtained from natural or recombinant sources, which proteins or peptides may be obtainable naturally or either chemically synthesized, or alternatively produced in vitro from recombinant host cells expressing DNA segments encoding such epitopes. Smaller peptides that include reactive epitopes, such as those between about 10 and about 50, or even between about 50 and about 100 amino acids in length will often be preferred. The antigenic proteins or peptides may also be combined with other agents, such as other peptide or nucleic acid compositions, if desired.

See Col. 12, lines 25-65 (emphasis added). Clearly, the reference directs the reader to the use of a CBP as a vaccine and does not disclose or suggest a method of making a human immunoglobulin composition as claimed in the present application, and indeed teaches one away from the present invention because it emphasizes and directs the reader to use the collagen binding protein as a means of generating an immune response.

Next, the Examiner asserts that Col. 67, lines 18-33 describe the ClfA peptide antigen for the generation and provision for passive immunization. This passage, repeated here below, has no such disclosure:

In vitro assays were performed to assess the impact of specific antibodies to collagen adhesion on phagocytosis and intracellular killing capacity. Collagen adhesion expressing Phillips strain was opsonized with either serum containing M55 specific antibodies or serum containing BSA antibodies, or alternatively serum from naive mice that have gone through infection with Phillips [described as a CBP+ strain].

The results (FIG. 5A) show clearly that intracellular killing of S. aureus Phillips strain is moderately enhanced by a previous infection with the same strain (p=0.037). In contrast, opsonization of staphylococci with

> serum from M55 mice immunized (but not infected) mice displayed significantly enhanced intracellular killing capacity as compared to control serum (p=0,009). The phagocytic capacity was only modestly affected by opsonization of bacteria with serum containing M55 antibodies and significantly affected when the bacteria were opsonized with serum of Phillips strain infected mice (FIG. 5B).

Moreover, the Examiner's reference to "passive immunization" with ClfA is based on sections 4.25 and 5.3.8 (presumably a reference to 5.3.7), but these sections (despite the titles) do no such thing and indeed merely disclose recombinantly making the protein (Section 4.25) or give the sequence for the protein (Section 5.3.7). In fact, the actual sequence given is the DNA sequence which includes the vector region which once again shows that the particular sequence is made recombinantly, not that it has been used in the preparation of any vaccine, much less the specific human immunoglobulin compositions of the present invention.

Next, the Examiner refers to immunization of donor mammals (Col. 61, lines 43-45 and 48-63) when in fact this is a polyclonal rabbit immunoglobulin and not a human immunoglobulin, and asserts that the Hook patent covers the steps as set forth in the claims, namely "immunizing and obtaining blood" (Col. 51, lines 26-27):; "recovering high titer" (Col. 51, lines 29-31); and "treating the blood to obtain purified immunoglobulin" (Col. 51, lines 34-35 and 39-48). See Official Action at Page 8. Once again, contrary to the Examiner's characterization, the disclosures referred to by the Examiner refer completely to an immunization of rabbits with CBP and have nothing to do with the method of making a human immunoglobulin composition based on the specific adhesins of the present claims. This cited disclosure at Col. 51 reads as follows:

> Rabbits were immunized with CBD (157-297) as described. Sera were also collected prior to immunization and tested for reactivity to CBD (151-297). The reactivity of the antiserum with different segments of CBD (151-297) was tested in an ELISA using a series of eight 25-amino-acid long synthetic peptides with partially overlapping sequences as targets. Purified IgG reacted strongly with peptides 2, 3, 5, 6, and 7 and weakly with peptides 1, 4, and 8. When preimmune IgG was tested with the CBD peptides, little reaction could be detected. The relative immunological reactivity of the different peptides correlated closely with their antigenic index using the algorithm of Jameson and Wolf (1988).
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> Purified α CBD(151-297) IgG inhibited the binding of *S. aureus* to 125 I-labeled Col in a dose-dependent manner. The amount of 125 I-Col bound by 10^8 bacterial cells was reduced over 50% by 5 μg and essentially completely inhibited by 10 μg of the purified immune IgG. Conversely, antibodies purified from preimmune sera did not possess significant inhibitory activity. These results suggest that the αCBD(151-297) antibodies recognize epitopes at or close to the active site of the MSCRAMM, thereby inhibiting or sterically interfering with Col binding.

Once again, the passage discloses and teaches the reader to immunize rabbits with CBP (or the collagen binding domain, CBD) in order to collect sera that contains antibodies to CBP which may inhibit or interfere with collagen binding. It clearly does not disclose or suggest the steps of the present application, namely the production of a human immunoglobulin composition with high titers to ClfA as set forth in the present application.

Accordingly, the rejection has been made by taking snippets here and there from various portions of a particular reference which, when examined, do not support the Examiner's rejection. Moreover, the reference when taken as a whole (even as reflected in the passages cited by the Examiner), clearly teaches one skilled in the art to use collagen binding proteins as active and passive vaccines, and teaches away from the present claims in which a human immunoglobulin composition is prepared which contains a high titer to ClfA.

Under the well established principles that are required to assert a rejection under 35 U.S.C. §103, this approach by the Examiner of picking and choosing just so much of a reference that allegedly supports a rejection has been expressly held as improper. As the Federal Circuit has stated, e.g., in the case of In re Hedges, 228 USPQ 685 (Fed. Cir. 1986), "it is impermissible within the framework of section 103 to pick and choose from any one reference only so much of it as will support a given position, the exclusion of other parts necessary to the full appreciation of what such reference fairly suggests to one of ordinary skill in the art." 228 USPQ at 687.

Still further, in light of the clear teaching of the Hook patent as set forth above, there would clearly be no motivation or suggestion to put the snippets together in the manner directed by the Examiner, particularly when the reference as a whole teaches one to utilize CBP as a vaccine to inhibit collagen binding. "Even when obviousness is based on a single prior art reference, there must be a showing of a suggestion or motivation to modify the teachings of that reference." In re Kotzab, 55 USPQ2d 1313, 1316-7 (Fed. Cir. 2000). In the present case, the passages cited by the Examiner when examined closely do not support the asserted positions, and in light of the clear teaching of the application away from Applicants' claimed invention, the various pieces of the application cannot be combined in the manner done by the Examiner, nor is there any motivation or suggestion to do so.

Accordingly, the Examiner's rejection on the basis of the Hook patent, insofar as applied to the claims as amended, is respectfully traversed and should be withdrawn.

It is thus clear that the claims as presently amended are not disclosed or suggested in the prior art references which did not relate to or suggest methods for preparing human immunoglobulin compositions in accordance with the present invention, and thus the Examiner's prior art rejections of the claims, insofar as applied to the claims as amended, are respectfully traversed and should be withdrawn.

The remaining objections of the Examiner are also overcome by the present Amendments. In particular, the objections to Claims 38-40 have become moot by the cancellation of these claims, and the language objected to by the Examiner has been removed from the new claims which incorporate this subject matter. Finally, without addressing the merits of the Examiner's double patenting rejections, these have been overcome by the filing of Terminal Disclaimers herewith.

In light of the amendments and arguments as set forth above, Applicants submit that the present application has now been placed in condition for allowance, and such action is earnestly solicited.

END OF REMARKS